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## REVIEW

# Laparoscopic nephroureterectomy for upper tract urothelial carcinoma – Update

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**Abstract** Upper urinary tract urothelial carcinomas (UTUCs) are uncommon and account for only 5%–10% of urothelial carcinomas. Pyelocaliceal tumors are about twice as common as ureteral tumors. Sixty percent of UTUCs are invasive at diagnosis. Radical nephroureterectomy, including the excision of the distal ureter and bladder cuff is standard of care for treatment of localized UTUCs, because of the high potential for recurrence, multifocality, and progression. Since first laparoscopic nephroureterectomy (LNU) was introduced by Clayman et al. in 1991 and improvement of laparoscopic technique and equipment, LNU has been reported to be equivalent to conventional open method. We reviewed the current literature of patients with UTUCs treated by LNU focusing on technical aspects, peri-operative and oncological outcomes. Laparoscopic radical nephroureterectomy offers the advantages of minimally invasive surgery without deteriorating the oncological outcome for treatment of UTUCs. Indications tend to increase as operator skills increase. Indications for laparoscopic or open nephroureterectomy are in principle the same. The basic requirement for laparoscopic surgery in UTUCs is to achieve benefits of minimal invasive surgery and maintain oncologic principles.

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## 1. Introduction

Upper urinary tract urothelial carcinomas (UTUCs) are uncommon and account for only 5%–10% of urothelial

carcinomas (UCs) [1]. About 60% of UTUCs are invasive at diagnosis compared with 15%–25% of bladder tumors [2].

Radical nephroureterectomy (RNU), including the excision of the ipsilateral distal ureter and bladder cuff

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(BCE), is the standard of care for treatment of localized UTUCs, because of the high potential for recurrence, multifocality, and progression. The first laparoscopic nephroureterectomy (LNU) was introduced by Clayman et al. in 1991 [3]. With the improvement of laparoscopic technique and equipment, LNU has been reported to be equivalent to conventional open method [4]. We reviewed the current literature of UTUCs treated by LNU and focused on the technical aspects, peri-operative and oncological outcomes.

## 2. Access of laparoscopy

During this contemporary 10-year study, minimal invasive nephroureterectomy (miNU) is replacing open surgery for UTUC [5]. LNU can be performed via a transperitoneal or a retroperitoneal access in a pure laparoscopic, hand-assisted or robotic-assisted laparoscopic technique.

Experienced surgeons may prefer the pure laparoscopic technique. The hand-assisted surgery represents a compromise between open and laparoscopic approach. The advocates of the hand-assisted technique emphasize the shorter learning curve of the procedure as well as the ability of palpation. This approach affords the use of tactile sensation, blunt manual dissection, and broad retraction with the manipulation. It also decreases operative time and allows surgeons to perform minimally invasive procedures for larger and more extensive tumors [6].

Recently, the da Vinci™ robot system (Intuitive Surgical, Sunnyvale, CA, USA) was introduced for surgeons to perform laparoscopic operations more easily by reducing the technical difficulty of intracorporeal suturing. The first case of robot-assisted NU (RANU) for left ureteral UC undergone via a retroperitoneal approach was reported by Rose et al. [7] in 2006. In recent, we observed that the practice of robot-assisted surgery in the treatment of many genitourinary diseases including UTUCs expanded extensively. The robot was most useful during the regional lymphadenectomy and suturing of the cystotomy after excision of the distal ureter [8]. However, the current data do not show any significant difference regarding peri-operative outcomes and postoperative morbidity when comparing these techniques.

As to the access of laparoscopy, the advantages of a transperitoneal approach compared to a retroperitoneal approach include a familiarity with anatomic landmarks and a larger working space. The retroperitoneal approach, however, has distinct advantages, including early control of the renal artery and vein, no manipulation of the bowel leading to less incidence of ileus and confinement of possible urinoma or seromas to the retroperitoneal space. As such, the retroperitoneal approach has the advantage in terms of quicker bowel recovery and shorter hospital stay [9]. More or less both transperitoneal and retroperitoneal laparoscopic approaches are considered as safe and effective methods for the treatment of UTUCs.

## 3. Distal ureterectomy and BCE techniques

The ideal nephroureterectomy procedure is to remove the entire ipsilateral urinary tract in continuity while avoiding

extravesical transfer of tumor-containing urine during the part of excision of bladder cuff, in an acceptable operative time with the least surgical complications [10]. Resection of the distal ureter and its orifice should be performed because there is a considerable risk of tumor recurrence in this area. After removal of the proximal ureter, it is difficult to image or approach it by endoscopy. Removal of the distal ureter and bladder cuff is beneficial after RNU [11,12]. However, the techniques of this part is the most diverse, thereby there is still lack of consensus regarding the optimal approach to the bladder cuff so far.

Several techniques for the resection of the distal ureter and bladder cuff have been described and they can be performed through a transvesical, extravesical, or endoscopic approach and the optimal approach still does not reach a consensus. Currently, these methods include open excision via a Gibson incision, transurethral resection (TUR) of ureteral orifice (pluck technique), ureteric intussusception, and pure laparoscopic or pure robotic-assisted laparoscopic resection techniques [13].

To compare the oncologic effectiveness of different surgical approach for BCE, Xylinas et al. [14] retrospectively analyzed 2681 patients who were treated with RNU with transvesical, extravesical, or endoscopic BCE. They found that there are no differences in extra-bladder recurrence and survival between transvesical, extravesical, and endoscopic management of the bladder cuff but the endoscopic approach results in higher intravesical bladder cancer recurrences. The transvesical approach guarantees precise distal ureter and BCE after preventive ureteral occlusion but it violates the bladder integrity in both cystotomy and BCE site in patients with a UTUCs. Therefore, an anterior cystotomy must be eschewed when there is an active bladder UC [15].

The pluck technique has been suggested to be oncologically safe in patients with proximal, low-grade UTUCs [12]. But this technique is not suitable for tumors or multifocal disease involving the lower ureter or the uretero-vesical junction or widespread carcinoma *in situ* due to the likelihood of tumor seeding, risk of local recurrence, and positive surgical margins [16]. Oncological concerns remain if the ureter is not occluded before resection, due to the risk of tumor spillage or retroperitoneal recurrences. To avoid these drawbacks, various modifications of ureteral occlusion have been suggested [17,18].

Pure LNU and RANU includes the techniques of laparoscopic dissection with either extravesical stapling of the distal ureter or complete laparoscopic dissection and resection of the whole kidney, ureter and bladder cuff, then suturing reconstruction of the bladder cuff area. The trocar configuration is similar to laparoscopic nephrectomy trocar deployment pattern, except that all the trocars are moved slightly caudally for better access to the distal ureter and bladder cuff.

Laparoscopic dissection with extravesical stapling of the distal ureter avoids cystotomy, however, this technique risks leaving viable ureteral mucosa and it may result in greater positive margin rate. In addition, staples may remain exposed within the bladder predisposing to stone formation, while the stapled margin cannot be assessed histologically [19,20].

Although robotics has enhanced the feasibility of performing a distal ureterectomy and proper BCE, the re-positioning, re-docking of the robot and in some instances, re-preparing the patient, all may result in a more lengthy operation.

Ritch *et al.* [21] performed a retrospective analysis on 36 patients comparing the open resection technique versus the laparoscopic extravesical stapling approach versus total laparoscopic dissection and suture reconstruction of ureter and bladder cuff. The results of this study showed that laparoscopic stapling and complete laparoscopic resection of distal ureter and suture reconstruction had significantly shorter operative time and hospital stay compared with the open resection technique. Nevertheless, a cystoscopically appreciable remnant of the resected ureteral orifice was noted in 50% of the laparoscopic stapling cohort versus none with the open resection or complete laparoscopic resection of distal ureter and suture reconstruction cohorts. The authors concluded that all patients with bulky distal ureter disease must continue to be treated with an open bladder cuff resection technique, while patients with low-stage, low-grade disease are preferentially treated with a total laparoscopic resection.

#### 4. Role of lymphadenectomy

Lymphovascular invasion (LVI) was considered as an independent predictor of poor outcome [22]. However, performing lymph node dissection (LND) is surgeon dependent. The templates for LND was suggested by Kondo and colleagues [23] according to the tumor location, and they interestingly found that in patients with muscle-invasive clinical node-negative UTUCs, the survival of the patients were influenced by the type of the templates but not the numbers of removed nodes.

To emphasize the importance of LND in the treatment of UTUCs, Abe *et al.* [24] retrospectively reviewed a cohort of 293 patients with UTUCs who underwent predominantly NU for localized disease. A total of 76 patients developed disease relapse. Regional lymph node recurrence was the most common site in 34 patients. On multivariate analyses that adjusted for the effect of tumor stage and tumor grade, pNx which meant that LND was not done during the procedure was an adverse factor not only for regional recurrence, but also for distant relapse. Even more, immunohistochemistry identified micrometastases in seven (14%) of 51 patients who were previously diagnosed as pN0 [24]. These findings further suggested a potential therapeutic benefit of LND by eliminating micrometastases.

However, in the study by Lughezzani and colleagues [25] analyzing 2824 patients from the SEER database, LND showed no benefit in patients with N0 status compared with Nx status. In addition, Roscigno *et al.* [26] addressed cancer-specific survival according to lymph node status at radical nephroureterectomy for UTUCs. They suggested that LND should be performed in patients with suspected pT2-4 stages, to improve the prediction of the natural history of surgically treated UTUCs and to use this information for possible adjuvant chemotherapy.

To conclude, the benefit of LND at RNU has been shown for locally advanced tumor stages and should be considered in all such cases [27]. Therefore, LND has been suggested to be curative in cases of limited nodal invasion and should be performed in patients with clinically positive regional nodal disease in the absence of distant metastases. Thus, the performance of LND *per se* seems to be prognostically beneficial.

The role of retroperitoneal lymph node dissection (RPLND) for UTUCs has been evolving in parallel with the technique of RNU. Melquist *et al.* [28] introduced single-docking RNU-RPLND, which offers a streamlined approach for this multicomponent operation, which may have broader implications in the oncologic management of patients. However, better designed prospective trials are still needed to standardize the indications for LND and to determine which lymph nodes should be removed according to different tumor locations within the urinary tract. Precise templates need to be established for each tumor location.

#### 5. Peri-operative outcomes

Benefits of minimally invasive surgery included less blood loss, decreased postoperative narcotic use, and shorter hospital stay [5]. Jens *et al.* [29] and Shaobin *et al.* [4] both reported a systemic review and cumulative analysis of available comparative studies on comparison of laparoscopic and open nephroureterectomy for UTUCs. The analysis revealed a slightly longer OR-time (276.6 vs. 220.1 min), and significantly lower blood loss (240.9 vs. 462.9 mL) in the laparoscopic series. No differences of minor (12.9% vs. 14.1%) or major complication rate (5.6% vs. 8.3%) were observed. Comparative studies revealed a significant dose reduction of the morphine-equivalents and shorter hospital stay after laparoscopy.

#### 6. Oncological outcomes

In early experience, it postulated initially that the high-pressure environment of the pneumoperitoneum might exacerbate tumor dissemination and result in a higher rate of recurrence [30]. There have been reports of retroperitoneal metastatic dissemination and/or dissemination along the trocar pathway when large tumors have been manipulated in a gas environment. Cases of peritoneal cancer dissemination or early metastases at unusual metastatic sites have been reported but always for high-grade invasive tumors [30].

However, recent advances in technology and experiences on laparoscopy have challenged the concepts. According to a systemic review and cumulative comparative studies, Jens *et al.* [29] reported that 21 eligible studies (1235 cases and 3093 controls) were identified. Although a significantly higher proportion of pTa/Tis was observed in LNU compared to open nephroureterectomy (ONU) (27.52% vs. 22.59%;  $p = 0.047$ ), yet there were no significant differences in other stages and pathologic grades (all  $p > 0.05$ ) [4]. In conclusion, there were no statistically significant differences in 2-year cancer specific survival, 5-year recurrence-free survival (RFS), 5-year overall survival (OS), 2-year OS, and metastasis rates [4,31].

## 7. Indications and contraindications

As in the majority series, predominantly non-invasive tumors (pTa/pT1) have been treated laparoscopically, and some recommend that invasive, large (T3/T4 and/or N+/M+), or multifocal tumors should be contraindications to LNU despite the eagerness of patients for minimally invasive surgery [32,33]. It is worth noting that indications tend to increase as operator skills increase. Oncological outcome of LNU is no inferior to that of ONU in muscle-invasive UTUC, when the appropriate patients are selected [34]. It indicated that the most important principle is to maintain oncologic principles and duplicate established open surgical techniques.

## 8. Conclusion

Laparoscopic radical nephroureterectomy offers the advantages of minimally invasive surgery without deteriorating the oncological outcome for treatment of UTUCs. Indications of LNU tend to extend to the advanced disease with the operator skills improving. The current challenges remain the choice of a way to undergo distal ureterectomy and BCE. The optimal approach depends on the experience of the surgeon and further confirmation about which is the best one still waits more clinical investigations.

## Conflicts of interest

The authors declare no conflict of interest.

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